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Opinion

First-trimester fetal echocardiography: routine practice or research tool?

First-trimester aneuploidy screening includes an ultrasound scan to measure nuchal translucency thickness. Some have used this opportunity to perform an extended fetal anomaly scan, including fetal echocardiography. However, as fetal medicine centers adopt non-invasive prenatal testing (NIPT) for aneuploidy screening, funding for first-trimester sonography may be reduced or disappear. It is timely, therefore, to review the contribution that early fetal echocardiography has made and to consider whether it should be funded in its own right in designated centers of excellence.

Early echocardiography has contributed to our understanding of disease prevalence as it may be performed before natural pregnancy loss or termination of pregnancy occurs. We have learned about structural and functional aspects of the early fetal heart: progression of malformations, associations with aneuploidy and maturation of function. It is now clear that while increased nuchal translucency is only modestly predictive of congenital heart disease (CHD), combining it with physiological measures such as tricuspid regurgitation and flow waveforms in the ductus venosus identifies a cohort at greater than average risk for CHD[1]. Only one third of first-trimester fetuses with trisomy 21 have CHD, which occurs most often in the female and in the form of an atrioventricular septal defect[2]. One postmortem study using histologically stained paraffin-embedded samples described a high prevalence of hypoplastic left heart syndrome in first-trimester fetuses with Turner syndrome – pathology that was previously unrecognized because of the high rate of spontaneous intrauterine demise of these fetuses[3].

First-trimester fetal echocardiography pioneers should be commended; however, adoption of this practice by others should be tempered with caution. Even in expert hands there is a relatively high false-positive rate compared to that in the second trimester, which, if taken in isolation, may lead to an increase in terminations of normal pregnancy. Certain pitfalls of early scanning have been recognized and it is important to be familiar with these when counseling families in early pregnancy. The marked cardiac disproportion seen in the first-trimester heart if there is an enlarged coronary sinus may not have any sinister implications for future growth of its left-sided structures.

For many families, the presence of aneuploidy is sufficient grounds for termination of the pregnancy and therefore the accuracy of early fetal cardiac diagnosis is difficult to confirm. Trisomy 21 is the most commonly observed aneuploidy and in one series[2] the rate of pregnancy termination was higher than 90%, so later verification of the cardiac diagnosis was unavailable. Moreover, this study found 10% of scans below 14 weeks to be non-diagnostic. There is a sound morphological basis for this, as demonstrated by the new postmortem technique, high-resolution episcopic microscopy (HREM), which has revealed many features of the first-trimester fetal heart previously unrecognized because of technical limitations. In HREM, the wax-embedded specimens are sliced more than 1000 times and each slice is photographed to enable creation of a three-dimensional volume set with a resolution of 0.5–5 μm[4]. In a sample of normal hearts retrieved following termination of pregnancy, this technology has revealed that growth of the atrioventricular septum occurs relatively late in the first trimester, with no offset of the mitral and tricuspid valves identifiable before 13–14 gestational weeks[5]. Even high-resolution four-dimensional (4D) transvaginal scanning of the first-trimester heart has a resolution of only 50–100 μm; thus, it is unlikely that the mild offset of the atrioventricular valves before 14 weeks can be diagnosed confidently and this may lead to an erroneous diagnosis of atrioventricular septal defect, even by an expert. In this issue, Votino *et al.*[6] caution that 4D spatiotemporal image correlation is not better than conventional two-dimensional ultrasound.

Where does this leave us? Two thirds of fetuses with major CHD have no extracardiac malformation or aneuploidy. Assuming that NIPT is about 98% accurate[7] and will identify an increasing range of aneuploidies, any future first- or early second-trimester echocardiography will be performed largely on fetuses that may have isolated CHD. Depending on the severity of the defect and local attitudes, this may result in termination of the pregnancy, but how confident can families be that a true cardiac anomaly is present so early in pregnancy? Because of high termination rates many first-trimester cardiac studies have very limited follow-up, below 20%, and so true quality assurance is not known[8].

Also in this issue, Zidere and colleagues[9] demonstrate their expertise in first-trimester diagnosis in continuing pregnancies scanned at least 6 weeks later, and report impressive sensitivity and specificity. However, if fetuses with resolving mild functional abnormality are removed from the denominator, 7/81 (9%) had a false-positive diagnosis of CHD. A further 15/81 (18.5%) had important discordant findings at the second-trimester scan, with 10/15 thought to be due to progression of disease that led to an alteration in counseling. Thus, even in expert hands, over 27% of important fetal

structural CHD were missed or the parents were counseled inappropriately for the eventual outcome. Clearly, this is not an activity for the faint-hearted.

Such concerns about the quality of information that can be obtained from the early human heart in euploid fetuses should make us pause to reconsider echocardiography in the first trimester and perhaps defer it until later in pregnancy.

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